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(71) Applicant: **SUMITOMO ELECTRIC INDUSTRIES, LIMITED**
5-33, Kitahama 4-chome Chuo-ku
Osaka(JP)

(72) Inventor: **Kanda, Masahiko**
Osaka Works of Sumitomo Electric Industries, Ltd.
1-3 Shimaya 1-chome Konohana-ku
Osaka(JP)

(74) Representative: Herrmann-Trentepohl, Werner, Dipl.-Ing. et al
Kirschner, Grosse, Bockhorni Forstenrieder Allee 59
D-8000 München 71(DE)

(54) Liver function testing apparatus.

(57) A liver function testing apparatus measures values $\log T_1$ and $\log T_2$ corresponding to pulse wave signals obtained upon passage through a prescribed optical path in vital tissue n times when a sensor (30) formed by first and second light sources (3, 4) and a light receiving element (6) is attached to a testee (5) before injection of a specific dye. A value α_0 is evaluated by two-variable statistical computation as to n $\Delta\log T_1$ and n $\Delta\log T_2$ on the basis of an operation expression of $\log T_1 = \alpha_0 \log T_2$, and $\Delta\log T_1$ and $\Delta\log T_2$ corresponding to pulse wave signals are measured in response to intensity levels of first light and second light reflecting the vital tissue from injection to a prescribed time on the basis of decision outputs of levels of the first light and the second light from the light sources after the specific dye is injected. A value Cg corresponding to specific dye concentration in blood is operated from α_0, $\Delta\log T_1$ and $\Delta\log T_2$, and a function of a simulation curve in time changes of the result of the operation is operated through least square fitting, thereby to obtain a blood plasma disappearance rate K and a T-minute retention rate R % of the specific dye on the basis of the function.

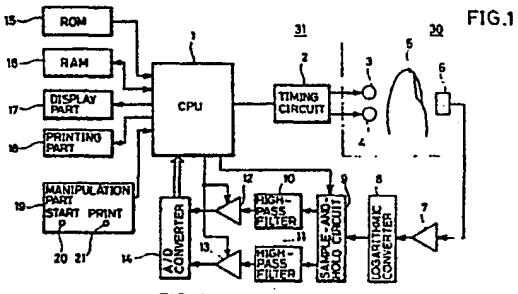


FIG.1

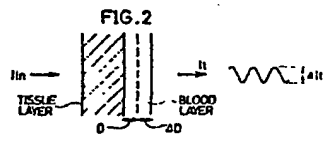


FIG.2

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Liver Function Testing Apparatus

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a liver function testing apparatus. More specifically, it relates to a liver function testing apparatus for automatically perf orming measurement for testing/diagnosing liver function by injecting a specific dye, which is selectively taken in and removed by only the liver, into blood and measuring a blood plasma disappearance rate and a retention rate thereof.

Description of the Prior Art

In general, the blood plasma disappearance rate and the retention rate have been measured by a method of blood sampling through use of indocyanine green (hereinafter referred to as ICG) serving as a specific dye.

According to this method, a tester intravenously injects ICG into an elbow vein, for example, of a testee with an injector to perform blood sampling three times after lapses of 5, 10 and 15 minutes from the injection, and separates blood serum upon coagulation of blood clot to measure absorbance at a wavelength of 805 nm through a spectrophotometer and obtain ICG concentration values in the blood serum after the lapses of 5, 10 and 15 minutes from a previously obtained calibration curve (corresponding ICG concentration in blood vs. absorbance), thereby to calculate the blood plasma disappearance rate and the retention rate from changes of the concentration values. ICG is dissolved in a physiological salt solution or the like.

Japanese Patent Publication Gazette No. 58649/1985 has proposed a method of applying light through the body surface of an organism and measuring quantities of light of a wavelength having high ICG absorption sensitivity and that of a wavelength substantially having no such sensitivity, thereby to measure the blood plasma disappearance rate and the retention rate from time changes (dye disappearance curve) thereof without performing blood sampling.

However, although it is necessary to correctly measure the blood sampling times after injection in the conventional blood sampling method, the times have not been accurately measured in an actual test, while the operation for such measurement has been complicated. Further, the testee has been subjected to heavy mental and physical burdens by blood sampling. In an R_{MAX} measuring method of evaluating the blood plasma disappearance rate by performing measurement several times with changes in ICG dosages, which method has been widely employed in recent years, blood sampling is performed ten or more times, to further increase the burdens on the testee.

In the aforementioned method of performing measurement without blood sampling, which is disclosed in Japanese Patent Publication Gazette No. 58649/1985 or Japanese Patent Laying-Open Gazette No. 162934/1986, the output of a sensor actually attached to an organism is fluctuated by influences such as blood flow disturbance caused by suppression on a blood vessel, vibration of the organism, which is the object of measurement, pulsation in the organism, changes of blood volume in the organism (the blood volume is changed by merely vertically moving an arm, for example) etc., and hence a correct dye disappearance curve cannot be obtained. Thus, the blood plasma disappearance rate and the retention rate obtained by the curve cannot be recognized as being correct.

Further, there is disclosed a method of measuring ICG concentration in blood by employing widths between peaks of changes in quantities of light beams of two wavelengths caused by pulse waves through an optical blood measuring apparatus described in Japanese Patent Laying-Open Gazette No. 128387/1975 or an oximeter described in Japanese Patent Laying-Open Gazette No. 88778/1978 as another method of performing measurement without blood sampling. However, such widths of changes in quantities of light cannot be correctly measured due to vibration of the organism etc., and it has been impossible to obtain a correct dye disappearance curve.

SUMMARY OF THE INVENTION

Accordingly, a principal object of the present invention is to provide a liver function testing apparatus which can remove artifacts such as blood flow disturbance, vibration of an organism, pulsation in the organism and changes of the blood volume in the organism caused in attachment of a sensor to the organism, to enable correct measurement.

Briefly stated, a sensor formed by light sources and a light receiving element is attached to a testee before injection of a specific dye, to measure values $\Delta\log T_1$ and $\Delta\log T_2$ corresponding to pulse wave signals obtained upon passage through a prescribed optical path in vital tissue n times. Then a value α_0 is evaluated by two-variable statis-

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tical computation as to n $\Delta logT_1$ and n $\Delta logT_2$ on the basis of an operation expression of $logT_1 = \alpha_c logT_2$, and in response to decision outputs of levels of respective light beams emitted from the light sources, $\Delta logT_1$ and ΔogT_2 corresponding to the pulse wave signals are measured on the basis of intensity levels of first light and second light reflecting the vital tissue from injection to a prescribed time after the specific dye is injected. A value Cg corresponding to specific dye concentration in blood is operated from α_0, $\Delta logT_1$ and $\Delta logT_2$, and a function of a simulation curve in time changes of the operation result is operated through least square fitting, to output operation results of a blood plasma disappearance rate K and a T-minute retention rate R % of the specific dye on the basis of the function.

According to the present invention, therefore, time management of a correct specific dye disappearance curve is enabled, whereby correct data can be obtained. Further, the blood plasma disappearance rate K and the T-minute retention rate R % can be obtained not from several samples prepared according to the conventional blood sampling method but from a large number of disappearance curve data, thereby to improve reliability of the data. In addition, the method of measurement can be further simplified as compared with the conventional testing method of obtaining the blood plasma disappearance rate K and the T-minute retention rate R % by performing measurement three times with changes of ICG dosages. Further, the problematic artifacts such as blood flow disturbance, vibration of an organism, pulsation in the organism and changes of the blood volume in the organism caused upon attachment of a sensor to the organism can be removed, to enable correct measurement. Thus, the present invention is effectively applicable to the overall field of measuring a dye in an organism with no invasion.

In a more preferred embodiment of the present invention, $\Delta logT_1$ and $\Delta logT_2$ are measured m times as operation values Cg(T) assuming that $\Delta logT_1$ and $\Delta logT_2$ represent values corresponding to pulse wave signals of intensity levels of first light and second light passing through a prescribed optical path in vital tissue, and a value $\alpha(t)$ is evaluated as to m x 2 by two-variable statistical computation of $\Delta logT_1 = \alpha(t) \bullet \Delta logT_2$, to obtain $Cg(t) = \beta(\alpha(t) - \alpha_0)$.

In the preferred embodiment, further, the function Cg of the operated simulation curve is:

$Cg = A \bullet e^{Bt}$

where

Cg: operation value

t: elapsed time (min.) after injection of specific dye

A, B: constants

The blood plasma disappearance rate K and the T-minute retention rate R % are obtained from:

$K = -B$

$R\ \% = e^{Bt}$

assuming that the elapsed time after injection, which characteristically expresses intake of the specific dye in the liver, is T minutes.

These and other objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of the present invention when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic block diagram showing an embodiment of the present invention;

Fig. 2 illustrates incident light applied to an organism and transmitted light;

Fig. 3 illustrates changes in quantity of light corresponding to a pulse wave;

Fig. 4 illustrates changes of $\Delta logT_1$ and $\Delta logT_2$ expressed on x and y coordinates;

Figs. 5 and are flow charts for illustrating concrete operation of the embodiment of the present invention;

Fig. 7 is a waveform diagram showing voltages corresponding to pulse waves; and

Fig. 8 illustrates an exemplary ICG disappearance curve.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Fig. 2 illustrates incident light which is applied to vital tissue and transmitted light, Fig. 3 illustrates changes in quantity of light corresponding to a pulse wave, and Fig. 4 illustrates changes of $\Delta logT_1$ and $\Delta logT_2$ expressed on x and y coordinates.

With reference to Figs. 2 to 4, the principle of the present invention is now described. When incident light I_{in} is applied to an organism as shown in Fig. 2, absorbance A is expressed as $log I_t/I_{in}$, assuming that I_t represents the quantity of transmitted light. The organism is formed by a tissue layer and a blood layer as shown in Fig. 2, and the blood layer is formed by an arterial layer and a venous layer. The thickness of the arterial layer is changed by ΔD in response to pulsation (pulse wave) of the heart. The quantity I_t of the transmitted light is varied with this change. Therefore, the absorbance A is similarly changed by ΔA. Hence,

$\Delta A = \Delta log I_t \quad (1)$

Assuming that ΔA_1 and ΔA_2 represent changes of absorption quantities caused by pulse waves of a wavelength λ_1 largely absorbed by a specific dye

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and an unabsorbed wavelength λ_2,

$\Delta A_1 = (E_\beta' \cdot C_\beta + E_g' \cdot C_g) \cdot \Delta D$ (2)

$\Delta A_2 = E_\beta^{2'} \cdot C_\beta \cdot \Delta D$ (3)

where

E_β': absorption coefficient of blood at wavelength λ_i

E_g': absorption coefficient of ICG at wavelength λ_i

C_β: blood concentration

C_g: specific dye concentration

ΔD: change in thickness of blood layer

Assuming that the degree of oxygen saturation of the blood is constant,

$E_\beta' \cdot C_\beta \cdot \Delta D = \alpha_0 (E_\beta^2 \cdot C_\beta \cdot \Delta D)$ (4)

Hence , the above expression (2) is transformed as follows: $\Delta A_1 = K \cdot \Delta A_2 + E_g' \cdot C_g \cdot \Delta D$ (5)

Thus,

$Cg = (\Delta A_1 \ \Delta A_2 - \alpha_0) \cdot E_\beta^2 \ E_g' \cdot E_\beta$ (6)

$E_\beta^2 \ E_g'$ is a known constant amount, and C_β is interpreted as being constant as blood concentration. Further, K can be determined from relation between ΔA_1 and ΔA_2, since the equation (2) is expressed as:

$\Delta A_1 = E_\beta' \cdot C_\beta \cdot \Delta D$ (7)

before injection of the specific dye.

Hence, the specific dye concentration C_g in the blood can be evaluated by obtaining ΔA_1 ΔA_2 after injection of the specific dye.

Assuming that T_1 and T_2 represent quantities of transmitted light having the wavelength λ_1 and that having the wavelength λ_2 while ΔT_1 and ΔT_2 represent changes thereof caused by ΔD, the following equation results from the expression (1):

$\Delta A_1 \cdot \Delta A_2 = \Delta \log T_1 \cdot \Delta \log T_2 = \alpha$ (8)

Hence, the expression (8) may be solved to obtain α before injection of the specific dye and the expression (8) may be solved after injection of the specific dye, while Cg may be evaluated from the expression (6). In the oximeter described in the aforementioned Japanese Patent Laying-Open Gazette No. 88778/1978 etc., difference between peaks of changes in quantity of light corresponding to a pulse wave has been regarded as $\Delta \log T_1$, as shown in Fig. 3. However, this method can only prepare a sample corresponding to the cardiac cycle, and the above $\Delta \log T_1$ has been obtained by performing measurement several times and averaging the results in the actual circumstances.

According to the present invention, not the difference between the peaks is obtained but $\Delta \log T_1$ is set on the y-axis and $\Delta \log T_2$ is set on the x-axis as shown in Fig. 4, for example, so that changes of measured values are as shown in Fig. 4 respectively and move on the coordinates with inclination expressed by a straight line a before injection of the specific dye. This inclination is α_0 shown in the expression (6). Then, when the specific dye is injected, absorbance of λ_1 is changed to define a waveform corresponding to a pulse wave such as a, and the inclination is changed to define a straight line such as a. This inclination α is $\Delta A_1, \Delta A_2$ in the expression (6).

Hence, inclination $\alpha(t)$ can be accurately calculated by increasing the number of measurement samples of $\Delta \log T_1$ and $\Delta \log T_2$, thereby to enable comprehension of concentration changes of the specific dye at a high speed without depending on the cardiac cycle.

An embodiment according to this method is now described.

Fig. 1 is a schematic block diagram showing an embodiment of the present invention. Referring to Fig. 1, a liver function testing apparatus is formed by a sensor part 30 and a measurement processing part 31. The sensor part 30 includes a first light source 3, a second light source 4 and a light receiving element 6. The first light source 3 and the second light source 4 generate optical pulses of the wavelength λ having large absorbance with respect to the specific dye and the wavelength λ_2 having no such absorbance. The light receiving element 6 receives light beams, which are applied from the light sources 3 and 4 to vital tissue 5 to pass through a prescribed optical path. The light sources 3 and 4 are controlled by a timing circuit 2 on the basis of a command from a CPU 1 which is provided in the measurement processing part 31, to alternately generate the light beams in pulse operation.

The CPU 1 included in the measurement processing part 31 serves as arithmetic means. As hereinabove described, the CPU 1 supplies prescribed pulses to the light sources 3 and 4 through the timing circuit 2. The light beams emitted from the first and second light sources 3 and 4 pass through the prescribed optical path in the vital tissue 5 to be incident upon the light receiving element 6. A current generated from the light receiving element 6 is subjected to current-voltage conversion and amplified by an amplifier 7. The amplified signal is supplied to a logarithmic converter 8 to be subjected to logarithmic conversion, and supplied to a sample-and-hold circuit 9, to be separated into signals of the wavelengths λ_1 and λ_2. The separated respective signals of the wavelengths λ_1 and λ_2 are supplied to high-pass filters 10 and 11. These signals include components by pulse waves as well as changes of blood volume such as those in venous blood, to have large snaking components. Therefore, the high-pass filters 10 and 11 remove these components to output only pulsating components, which in turn are supplied to an A-D converter 14 through amplifiers 12 and 13. The amplifiers 12 and 13 are so controlled that amplification factors thereof are changed in response to control signals from the CPU 1. The A-D converter 14 converts the inputted signals into digital signals and supplies the same to

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the CPU 1. The CPU 1 stores the digital signals in a RAM 16.

The CPU 1 is connected with a ROM 15, the RAM 16, a display part 17, a printing part 18 and a manipulation part 19. The ROM 15 stores programs based on flow charts shown in Figs. 5 and 6 as hereinafter described. The manipulation part 19 includes a start key 20 and a print key 21. The start key 20 is adapted to command starting of a measurement mode, and the print key 21 is adapted to supply a command for printing out test results to the printing part 18.

Figs. 5 and 6 are flow charts for illustrating concrete operation of the embodiment of the present invention. Fig. 7 is a waveform diagram showing voltages corresponding to pulse waves, and Fig. 8 illustrates an exemplary ICG disappearance curve obtained in the case of employing ICG as the specific dye.

With reference to Figs. 1 and 5 to 8, concrete operation of the embodiment of the present invention is now described as to the case of employing ICG as the specific dye. At a step SP1 shown in Fig. 5, power is applied to the apparatus and then quantities of light are adjusted. That is, the CPU 1 supplies a command to the timing circuit 2 to adjust driving currents for the light sources 3 and 4 respectively, while adjusting the light receiving element 6 so that its output reaches a prescribed level.

Light beams emitted from the light sources 3 and 4 pass through a prescribed optical path in the vital tissue 5 to be incident upon the light receiving element 6, and a current generated from the light receiving element 6 is subjected to current-voltage conversion and amplified by the amplifier 7, to provide an output V_{PD} shown in Fig. 7. This signal is supplied to the logarithmic converter 6 to be subjected to logarithmic conversion, and separated into signals of the waveforms λ_1 and λ_2 by the sample-and-hold circuit 9. These signals are expressed as $\log T_1$ and $\log T_2$ in Fig. 7 respectively. These signals contain components by pulse waves as well as changes in blood volume such as those in venous blood etc., to have large snaking components, which are removed by the high-pass filters 10 and 11 so that only pulsating components such as $\Delta\log T_1$ and $\Delta\log T_2$ shown in Fig. 7 are extracted.

At a step SP2, the CPU 1 controls amplification factors of the amplifiers 12 and 13 to amplify the signals until widths between peaks of pulse wave corresponding voltages of $\Delta\log T_1$ and $\Delta\log T_2$ shown in Fig. 7 reach certain levels. Then, the CPU 1 calculates α_0 at a step SP3. In more concrete terms, the CPU 1 samples the signals of $\Delta\log T_1$ and $\Delta\log T_2$ n times at a step SP31 as shown in Fig. 6 and then performs regression analysis as to i = 1 to n through use of 2 x n data by an operation expression of $\log T_1(i) = \alpha \bullet \log T_2(i)$ at a step SP32 to calculate α, and stores the same in the RAM 16 as α_0.

Then, the CPU 1 displays indication such as "Inject ICG", for example, on the display part 17 at a step SP4. Thus, the operator prepares to inject ICG into the vein of the organism, and turns on the start key 20 of the manipulation part 19 simultaneously with ICG injection. The CPU 1 waits for entry of the start key 20 at a step SP5, and operates T-minute ICG concentration Cg in blood at a step SP6 when the start key 20 is operated. In more concrete terms, α at a certain time t is evaluated in accordance with the aforementioned flow chart shown in Fig. 6, thereby to obtain Cg from the above expression (6), supposing that α is $\Delta A_1/\Delta A_2$. The data of Cg draw an ICG disappearance curve as shown in Fig. 8, for example, and within the data, constants A and B are evaluated through least square fitting with a simulation curve of:

$Cg(t) = Ae^{Bt}$

$t = T_S(n - 1)$ (min.)

with respect to data between times T_1 and T_2 ($0 < T_1 < T_2 < T$).

Then, the CPU 1 operates a blood plasma disappearance rate $K = -B$ and a T-minute retention rate $R\% = e^{BT}$ at a step SP7, to evaluate K and R.

Then, the CPU 1 displays the disappearance curve shown in Fig. 8 and the values K and R on the display part 17, and outputs the same to the printing part 18 to print out the same at a step SP8.

The present invention can be also applied to an apparatus for measuring R_{MAX} by evaluating/calculating values K of various ICG dosages.

According to the present invention, as hereinabove described, optical pulses of a wavelength largely absorbed by a specific dye and optical pulses of a wavelength not absorbed by the same are applied to vital tissue at prescribed levels to detect optical pulses passing through a prescribed optical path in the vital tissue, and after the specific dye is injected on the basis of the outputs, a blood plasma disappearance rate and a retention rate of the specific dye are obtained on the basis of light receiving outputs from injection to a prescribed time in accordance with prescribed operation expressions. Thus, time management of a correct specific dye disappearance curve is enabled to obtain correct data.

Further, the blood plasma disappearance rate and the retention rate can be obtained not from several samples prepared by the conventional blood sampling method but from a large number of disappearance curve data, thereby to improve re-

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liability of the data.

In addition, the method of measurement can be further simplified as compared with the conventional testing method of obtaining the blood plasma disappearance rate and the retention rate by performing measurement several times with changes in ICG dosages.

Further, problematic artifacts such as blood flow disturbance, vibration of an organism, pulsation in the organism and changes of the blood volume in the organism caused in attachment of a sensor to the organism can be removed to enable correct measurement. Thus, the present invention is effectively applicable to the overall field of measuring a dye in an organism with no invasion.

The present invention is applicable not only to a liver function testing apparatus but to an apparatus, such as a pulse oximeter, for example, for measuring changes in concentration of a dye in an organism through pulse waves.

Although the present invention has been described and illustrated in detail, it is clearly understood that the same is by way of illustration and example only and is not to be taken by way of limitation, the spirit and scope of the present invention being limited only by the terms of the appended claims.

Claims

1. A liver function testing apparatus for testing liver function, comprising:
light source means (3, 4) for exposing vital tissue to first light of a wavelength absorbed by a specific dye dosed into blood of said vital tissue to be taken in and removed by the liver and second light of a wavelength not absorbed by said specific dye;
light receiving means (6) for detecting said first light and said second light from said light source means passing through a prescribed optical path in said vital tissue;
decision means (SP1) for deciding levels of said first light and said second light from said light source means in response to signals received by said light receiving means;
set means (SP1) for setting levels of said first light and said second light emitted from said light source means so that intensity levels of said first light and said second light passing through said prescribed optical path in said vital tissue upon attachment of a sensor formed by said light source means and said light receiving means to a testee are within prescribed ranges before injection of said specific dye;
set means (SP2) for logarithmically converting intensity values T_1 and T_2 of said first light and said second light passing through said prescribed optical path in said vital tissue, extracting only $\Delta\log T_1$ and $\Delta\log T_2$ corresponding to pulse wave signals, and setting maximum and minimum widths of said $\Delta\log T_1$ and $\Delta\log T_2$ within prescribed ranges before injection of said specific dye;
means (SP4) for informing timing for injecting said specific dye;
arithmetic means (SP3 to SP8) for measuring $\log T_1$ and $\log T_2$ corresponding to pulse wave signals obtained by passage through said prescribed optical path in said vital tissue upon attachment of said sensor formed by said light source means and said light receiving means to said testee n times to evaluate α_0 by variable statistical computation as to n $\Delta\log T_1$ and n $\Delta\log T_2$ on the basis of an operation expression of $\log T_1 = \alpha_0 \log T_2$ before injection of said specific dye, measuring $\Delta\log T_1$ and $\Delta\log T_2$ corresponding to said pulse wave signals on the basis of intensity levels of said first light and second light reflecting said vital tissue from injection to a prescribed time in response to outputs from said decision means after injection of said specific dye, operating a value Cg corresponding to specific dye concentration in blood from said α_0, $\Delta\log T_1$ and $\Delta\log T_2$, operating a function of a simulation curve in time changes of the result of said operation through least square fitting, and evaluating a blood plasma disappearance rate K and a T-minute retention rate R % of said specific dye on the basis of said function; and
output means (17, 18) for outputting the result of operation by said arithmetic means.

2. A liver function testing apparatus in accordance with claim 1, wherein said arithmetic means includes means for measuring $\Delta\log T_1$ and $\Delta\log T_2$ m times as operation values Cg(t) assuming that $\Delta\log T_1$ and $\Delta\log T_2$ represent values corresponding to pulse wave signals expressing intensity levels of said first light and said second light passing through said prescribed optical path in said vital tissue, evaluating $\alpha(t)$ as to m x 2 by two-variable statistical computation of $\Delta\log T_1 = \alpha(t) \bullet \Delta\log T_2$, and obtaining:
$Cg(t) = \beta(\alpha(t) - \alpha_0)$
where β represents a constant.

3. A liver function testing apparatus in accordance with claim 1, wherein a function Cg of said simulation curve operated by said arithmetic means is:
$Cg = A \bullet e^{Bt}$
where
Cg: operation value
t: elapsed time (min.) after injection of specific dye
A, B: constants
said apparatus further including means for obtaining said blood plasma disappearance rate K and said T-minute retention rate R % from:
$K = -B$

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$R\% = e^{Bt}$

assuming that an elapsed time upon injection, which characteristically expresses intake of said specific dye in the liver, is T minutes.

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FIG.1

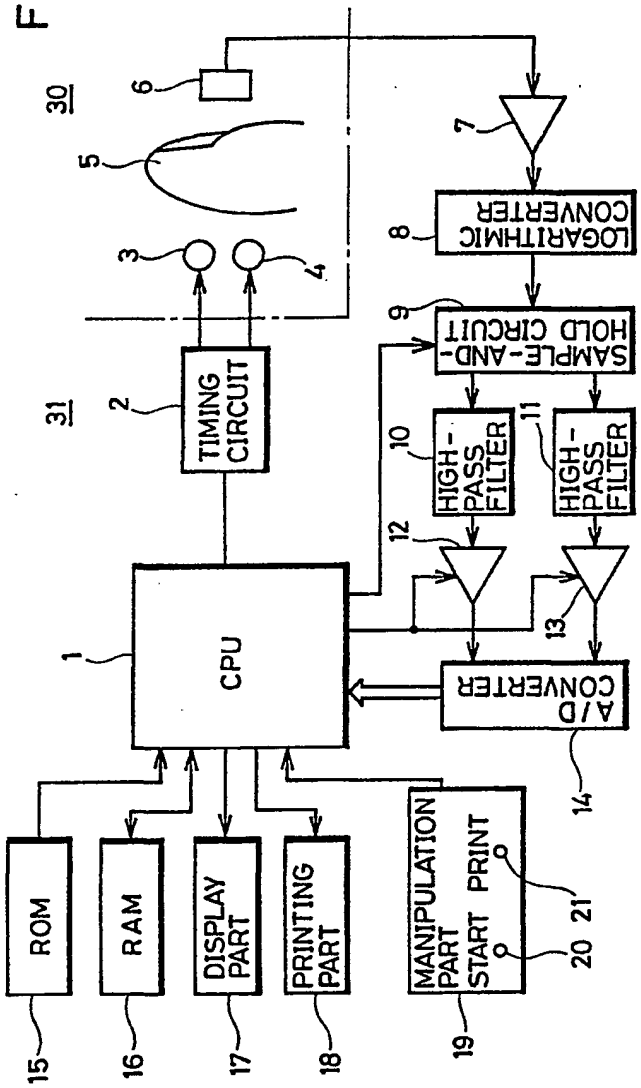

30
31
6
5
3
4
7
8
LOGARITHMIC CONVERTER
9
SAMPLE-AND-HOLD CIRCUIT
2
TIMING CIRCUIT
10
HIGH-PASS FILTER
11
HIGH-PASS FILTER
12
13
1
CPU
A/D CONVERTER
14
ROM
RAM
DISPLAY PART
PRINTING PART
MANIPULATION PART
START
PRINT
20
21
15
16
17
18
19

FIG.2

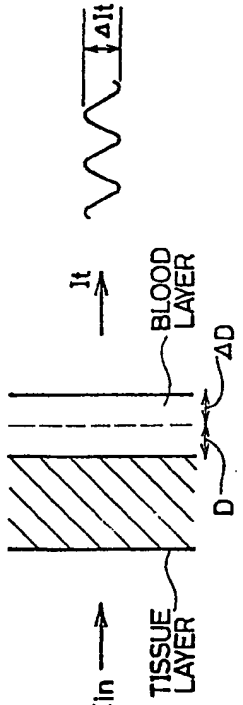

Δlt
lt
BLOOD LAYER
ΔD
D
lin
TISSUE LAYER

FIG.5

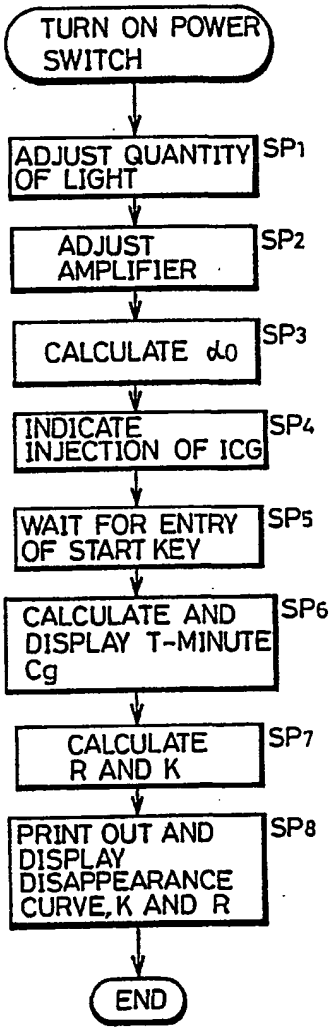
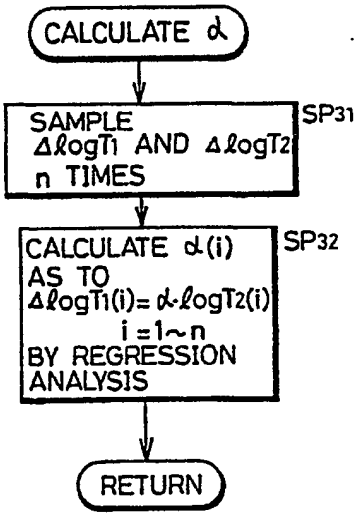


FIG.6



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FIG.3



FIG.4

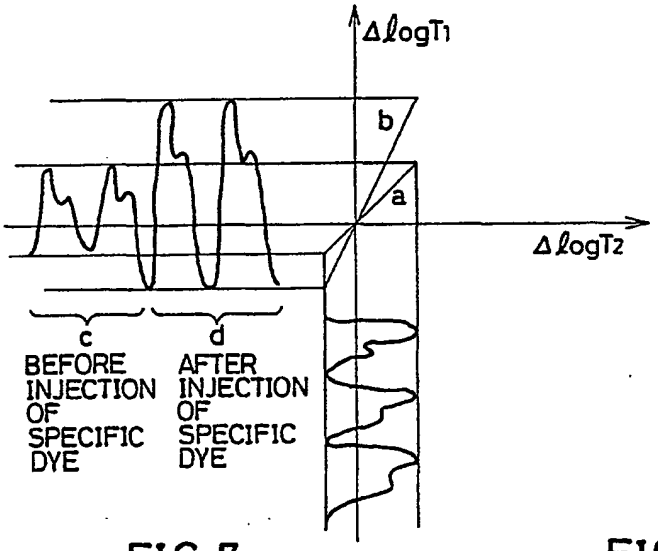


FIG.7

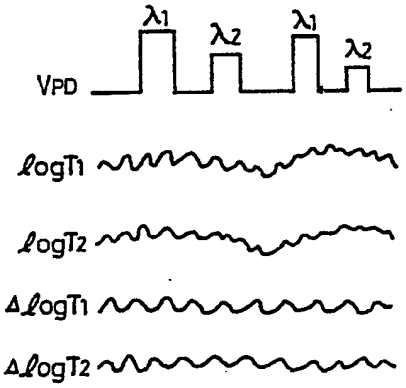
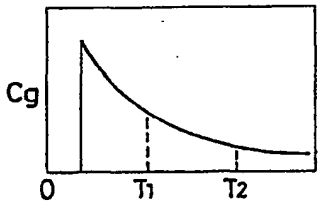


FIG.8



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